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RE: Comments on JNCI Papers

In response to your request, I am pleased to provide comments on two papers recently published in the Journal of the National Cancer Institute (Attfield et al.[1] and Silverman et al.[2]).

These papers address the possible association between exposure of miners to diesel exhaust and an increase in lung cancer. These papers are of special interest to New Mexicans because the papers utilize data on miners working in three potash mines in New Mexico. The papers are part of a series of investigations that began in the 1980s. A detailed protocol for the Diesel Exhaust in Miners Study (DEMS) was developed in the mid-1990s by the National Institute of Occupational Safety and Health and the National Cancer Institute. The protocol[3] released in 1997 heightened interest in DEMS because it indicated that special attention would be directed to characterizing exposure to diesel exhaust, especially to diesel exhaust particles. These particles consist of clusters of many very small elemental carbon particles and absorbed organic compounds. The lack of exposure characterization data was a serious weakness in previous epidemiological studies of diesel exhaust.[4]

By way of background, an epidemiological study may be viewed as being analogous to a three-legged stool. The three legs being (a) an exposure assessment for the population being studied, including exposure to confounding agents such as cigarette smoke, asbestos, radon, etc., (b) health data, both morbidity (sickness) and mortality (deaths by cause) on the population, and (c) the analytical procedures, which today includes complex computer-based statistical programs used to analyze the relationship between exposure and health outcome, for example, lung cancer. A well-conducted epidemiological study is dependent on all three legs being solid. Moreover,

the entire data set from exposure to vital health statistics should be sufficiently robust that other investigators can replicate the findings and, indeed, explore alternative analyses.

NIOSH-NCI has been promising for about 10 years to release for publication papers from DEMS. Five papers[5,6,7,8,9] characterizing exposure in the mines appeared in 2010 and 2011. The contents of these papers were in some cases at variance with the original 1997 protocol[3] and raised concern as to how well diesel exhaust exposure was characterized in the 8 mines. These concerns were published[10] and, in turn, led to concern for possible flaws in any epidemiological studies using the exposure data. The five papers[5-9] contain information obtained from measurements made at various times from 1976 through 2001. A key set of data were obtained in 1998-2001 specifically for DEMS and are a linch pin in the evaluation. I view these data as the linch pin data set since considerable emphasis was given to monitoring Respirable Elemental Carbon (REC) and the 1998-2001 data were to be used to interpret earlier data dating to 1996.

The epidemiological papers[1,2] use REC as a measure of miner exposure and lead the reader to think that the REC, the primary exposure estimates are very solid. Indeed, the Attfield et al. paper[1] notes "the exposure assessment relied on thousands of recent and historical measurements." In my opinion, this is a very misleading statement. As reported in Stewart et al. (2010)[5] a total of 37,269 measurements were made of 14 different agents. It is remarkable that only 1457 measurements were of REC out of the 37,269 measurements. A total of 11,170 were measurements of Carbon Monoxide (CO) of which more than half were below detection limits. One of the New Mexico Potash mines included in the study was closed in 1995 so measurements could not be made in it in 1998-2001. It is remarkable that they used measurements made in another New Mexico Potash mine to estimate prior exposures in the closed mine. I do not have any confidence in that kind of extrapolation

A major concern is that the NIOSH/NCI investigators used the CO measurements and estimates of the Horse-Power (HP) of equipment in use in various years to <u>estimate</u> REC exposure. In my opinion, the exposure leg of the epidemiological stool I noted earlier is very likely seriously flawed as already pointed out by others (Borak et al.)[10].

I am eager to see if other investigators can reproduce the NIOSH/NCI exposure assessment. Unfortunately, NIOSH/NCI have not yet released the total exposure data set so it has not been possible for other investigators to attempt to replicate the findings. I am

particularly concerned about the numerous extrapolated REC values based on CO and HP for two reasons. First, the fact that over half the CO values were below detection limits. Second, because of the high degree of uncertainty in the relationship between CO and REC. It is well known that the relationship between CO and REC is quite variable dependent on the particular engine and whether oxidation catalysts were used to remove CO.[11]

The second leg of the stool, the mortality data (Vital Statistics) is also of concern. Mortality of the miners was ascertained through December 31, 1997. A major concern is the validity of the cigarette smoking histories which were largely obtained from next of kin. Cigarette smoking is the major cause of lung cancer. Silverman et al.[2] reported Odds Ratios (OR) for current, 2 packs per day or over for "surface workers" of 26.60 and for "ever underground workers" of 7.13. The basis for the differences was not adequately explained. Any errors in the smoking history of individuals will result in errors in estimating the hazard of diesel exhaust exposure.

The third leg of the stool, the methodology, is also of concern. A major concern is that a number of the analyses reported did not follow the original protocol (a priori analyses). It appears the authors ignored the original data analysis plans and instead rely heavily on data driven (a-posteriori) analyses. This raises questions as to any arbitrary selection of results for presentation. It is important to note that Attfield et al.[1] reported – "Initial (i.e. a prior defined) analyses from the complete cohort did not reveal a clear relationship of lung cancer mortality with DE exposures." This is a very revealing statement and suggests that all of the reported findings of an association between estimated diesel exhaust exposure and lung cancer were a posteriori analyses. Perhaps this is why it took 15 years to complete the study.

The bottom line is that I have serious concerns about the results presented in Attfield et al.[1] and Silverman et al.[2]. My major concerns are outlined above, however, I have many other concerns related to the manner in which the analyses were conducted and presented. Some of the findings are simply inconsistent with earlier reports.[4]

There is a critical need for NCI-NIOSH to make the entire data set available to qualified investigators to attempt to replicate the reported results and then proceed to more rigorous analyses. I suggest that a high degree of caution should be exercised in interpreting the results of Attfield[1] and Silverman et al.[2] until the data have been rigorously analyzed by other investigators. In my opinion, all three legs of the stool I referred to earlier as under-girding a

well-conducted epidemiological study are open to serious question in the case of the NCI-NIOSH studies.

On a good news note, it is important to note steady progress has been made in reducing diesel exhaust exposures in underground mines. Moreover, new diesel technology (use of ultra-low sulfur fuel, improved engine design and control, exhaust after-treatment, wall-flow filters and oxidation catalysts) has resulted in marked reductions in emissions of diesel exhaust particulates (DEP). All on-road equipment sold in the USA in 2007 and later must meet very stringent new particulate emission standards. Emissions of DEP have been reduced to less than 1% of the levels typical of 2000 and earlier from traditional diesel engines using high sulfur fuel.

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